

A single nucleotide polymorphism in codon F31I and V57I of the *AURKA* gene in invasive ductal breast carcinoma in Middle East

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Abstract

Although few studies have suggested a carcinogenic role for polymorphism of F31I and V57I codons of *AURKA* gene in invasive ductal carcinoma, contradictory results from different populations mandates regional investigations. We aimed to determine polymorphisms of F31I and V57I codons of *AURKA* gene and their association with cancer prognosis in patients compared with controls in an eastern population of Iran.

A case-control study was conducted on specimens from 100 patients and 100 age- and gender-matched controls. DNA was extracted and the codons F31I and V57I were amplified. The different genotypes were analyzed by PCR-RFLP and electrophoresis.

In codon F31I, the frequency of Phe/Ile was 70% and 82% in patients and healthy controls respectively, whereas (Ile/Ile) was 30% in patients and 18% in healthy ($P = .047$). Analyzing V57I genotypes showed a higher homozygote Val/Val genotype in patients compared with controls (76% vs 68%), whereas the frequency of heterozygous Val/Ile genotype was lower in patients (17%) than controls (30%), yielding a marginal association between breast cancer and Val/Val genotype ($P = .048$). No association was observed between SNPs of either F31I or V57I genotypes and histological grades. However, there was a significant association between tumor stages and F31I genotype (P for trend = .003).

This is the first report of F31I and V57I polymorphisms in *AURKA* gene in breast cancer in Iran. Determination of allelic polymorphism of those codons will help to understand background genetic predisposition and could have prognostic value in management of breast cancer in the target population.

Abbreviations: PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism analysis.

Keywords: *AURKA* gene, breast cancer, F31I codon V57I codon, invasive ductal carcinoma

1. Introduction

Breast cancer is common, with about 1.7 million new cases and more than 0.5 million deaths in 2012^[1]; its incidence is increasing.^[2] The average age at diagnosis is relatively low in some regions in Iran.^[3] Resistance to chemotherapy in breast cancer may be due to genetic and epigenetic changes in metastatic breast cancer.^[4]

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The aurora kinases regulate important events in the cell cycle. Aurora A kinase is encoded by the gene *AURKA*, also known as STK15 (serine/threonine kinase 15).^[5] It regulates the G2 to M transition into mitosis. Nonsynonymous *AURKA* polymorphisms (91T/A and 169G/A) encode phenylalanine/isoleucine (F31I) and valine/isoleucine (V57I). These polymorphisms have been linked with cancers, including breast cancer, identifying *AURKA* as a possible oncogene/cancer susceptibility gene. *AURKA* is located on chromosome 20 (20q13.2). Its product is a protein of 403 amino acids with regulatory and catalytic domains.^[6,7] The catalytic domain has a serine/threonine kinase activity role. *AURKA* may be amplified and is overexpressed in many malignancies including invasive carcinomas of ovary, head and neck, and breast.^[8–10] Overexpression mechanisms and effects of *AURKA* in carcinomas are not yet fully understood. Aurora kinase A controls cell cycle checkpoints and has roles in centrosome division, cytoskeleton, and cytokinesis. Overexpression may cause genomic instability via dysregulation of the cell cycle, leading to tumor development.^[11,12] *AURKA* has been investigated as a drug target in many animal-model trials.^[13,14]

Many studies have suggested that both polymorphisms (F31I and V57I) are associated with risk of breast cancer.^[15–18] Cox et al found an association between breast carcinoma and F31I and V57I homozygote alleles in postmenopausal women in the USA.^[16] Similar findings have been discussed by Ewart-Toland et al who identified *AURKA* as a low-penetrance tumor-susceptibility gene in mice and humans.^[17] Sun et al found that aurora A kinase Ile/Ile 31 homozygosity was associated with

increased risk of breast carcinoma in an Asian population.^[18] A meta-analysis by Dai et al found the isoleucine-encoding AURKA polymorphism rs2273535 T/A (Phe31Ile) increased the risk of breast cancer in Asians but not Caucasian) while the isoleucine-encoding rs1047972 G/A Val57Ile polymorphism reduced breast cancer risk in Caucasians but not Asians.^[19] There remains a need for further data on the contribution of AURKA single nucleotide polymorphisms to breast cancer risk in different human populations, some of which are very poorly represented in the published literature.

Furthermore, few studies anywhere have examined the possible interactions of the SNPs responsible for the F31I and V57I aurora A kinase polymorphisms with important pathological determinants of breast cancer behavior in different populations. This study is the first attempt to investigate the polymorphisms in SNP of F31I and V57I codons of AURKA gene in breast cancer in Iranian patients, including their prognostic value.

2. Methods and materials

In this case-control study, 100 women with breast cancer and 100 healthy controls were compared. The 2 groups were age-matched with comparable age (mean 47.3 ± 12.8 and 48.1 ± 12.5 years, respectively).

2.1. Histopathological studies

Representative tissue samples were collected from 100 women diagnosed with invasive ductal carcinoma between 2011 and 2015 in the main hospitals of Sabzevar district, North-East Iran. Samples including tumor tissue were taken for diagnosis and treatment.

The typical surgical specimens were ranged 10 to 25 mm in size. All parts of tumor were cut and blocked sequentially every 2 mm in paraffin wax according to our standard practice protocol of histopathology irrespective of the tumor size. Each block was then sectioned into 5- μ m thick tissues to mount on slides. The 5- μ m sections stained with hematoxylin and eosin were assessed by 2 expert pathologists. The pathologists classified each carcinoma using standard criteria for stage and grade. Grade (from 1 to 3) was based on mitosis counts, nuclear pleomorphism, and acinar differentiation. The presence or absence of necrosis, maximum size of the lesion, and surgical margins were also recorded. Staging employs the standard TNM system.

2.2. DNA extraction

DNA was extracted using a standard kit (QIAGEN, Manchester, UK). Peripheral blood samples were collected from all healthy controls in 1.5 mL tubes containing 0.5 mM EDTA and stored at -20°C or -70°C until required. Stored blood was thawed and diluted with PBS and cells were separated by Ficoll-Hypaque gradient centrifugation. Prepared blood samples from healthy control were used for polymerase chain reaction restriction fragment length polymorphism analysis (PCR-RFLP). For patients, 5- μ m tumor sections were deparaffinized for DNA extraction. We used spectrophotometer UV and gel electrophoresis to assess DNA quality.

2.3. Polymerase chain reaction restriction fragment length polymorphism analysis

Codons F31I and V57I of AURKA exon 4 were amplified, using lyophilized primers diluted to 5 mM dNTP (stock 10 mM) with

deionized sterile water, according to manufacturer's instructions (Genet Bio, South Korea). The primer sequences were as follows:

Forward: CTTTCATGAATGCCAGAAAGTT and Reverse: TCTGCTTCTTCTGATTCTGAACC.^[6]

Annealing at 53°C for 60 seconds for 38 amplification cycles gave optimal amplification (Astech, Japan). Each tube for polymerase chain reaction (PCR) composed of 2.5 μ L $10\times$ buffer, 0.8 μ L of each primer, 5 μ L of DNA, 0.5 μ L of dNTP, 2.5 μ L of magnesium chloride, and DNA polymerase enzyme at 0.2 μ L which were diluted to the final volume of 25 μ L using distilled water.

A standard electrophoresis protocol was performed using 1.5% agarose gel, 5 μ L of each PCR product and 1 μ L of loading dye for each, well stained with ethidium bromide (EtBr). Electrophoresis photographs were taken by gel documentation machine (Bio-Rad, Hercules, CA).

2.4. Restriction fragment length polymorphism analysis

For determination of genotype (polymorphism) of PCR products, restriction fragment length polymorphism analysis (RFLP) was performed using 2 different enzymes, ApoI and BstUI. With either XapI (ApoI) or BstUI at 2 μ L, a solution composed of Tango $10\times$ buffer 2 μ L, nuclease-free water 18 μ L, and PCR reaction mixture 10 μ L (Thermo Scientific, Lithuania) was used. All samples were incubated at 37°C for 2 hours. They were then run on 2.5% agarose gel and photographs taken after completion.

2.5. Statistical analyses

To compare the proportion of cases and controls with a specific polymorphism, Chi square and Fisher exact tests were used. The trend of associations between cancer stages and either F31I or V57I polymorphisms were tested using cross-tabulations and *P* for trend test. For analysis of survival rate, survival distribution and their associations Kaplan-Meier and log-rank tests were performed. Differences between cases and controls were taken as significant if $P < .05$ (2-sided probability). To have an estimate of sample size in original plan, assuming presence of Phe/Ile genotype of codon F31I in 85% of controls and 65% of cancer population, 0.05 type I error and 0.80 type II error, minimum sample size were 82. Data was analyzed using IBM SPSS package version 22 (IBM UK, Hampshire, England).

2.6. Ethical considerations

The protocol of the study has been reviewed by medical ethics committee of Sabzevar University of Medical Science and has been approved under Medsab.IR.REC.1393.16. This study used project-specific resources and investigators have rights to share relevant data after examining the potential collaboration projects by the relevant research committee.

3. Results

3.1. Demographic data

The present study was conducted on 200 women: 100 with in situ or invasive ductal breast carcinoma (mean [\pm SD] age 47.25 ± 12.80 years). The healthy control group were age-matched women (mean [\pm SD] age of 48.08 ± 12.50 years). The age range was 25 to 86 years for patients and 23 to 80 years for healthy controls.

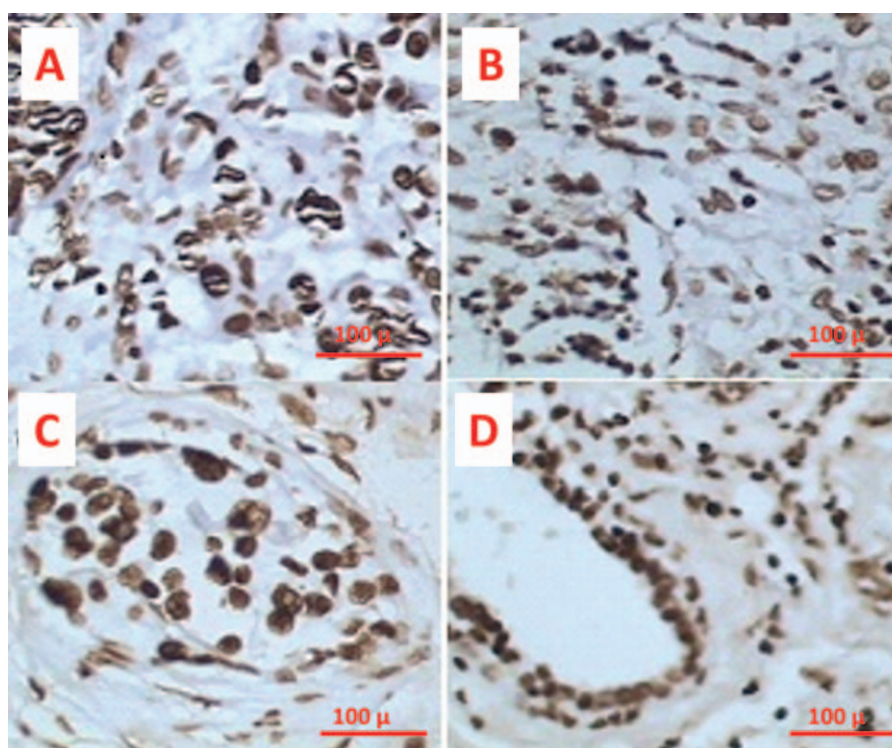


Figure 1. The figure shows 5 μ sections from both malignant and healthy tissues. (A) Grade 3 with frequent mitotic and polymorphic brownish color cells. No nodular differentiation observed. (B) and (C) show grade 2 and 1, respectively, whereas (D) shows healthy cells and tissue (magnification of all original images: 400 \times).

3.2. Histopathological findings

3.2.1. Grade. There were 19 (19%) grade 1 carcinomas, 51 (51%) grade 2, and the remaining 30 (30%) were grade 3 (Fig. 1).

3.2.2. Stage. There were 37 cases in disease stage of 0 (carcinoma in situ) or I, of which 11 samples had in situ carcinoma only, whereas 26 were stage I invasive carcinomas without lymph nodes involvement.

In 39 cases, lymph nodes or adjacent tissues were involved (stage II). In 13 cases, the cancer spread to internal mammary lymph nodes; in some cases even the chest wall was invaded (stage III). In the remaining cases of invasive ductal carcinoma, 11 cases were at stage IV (metastatic).

3.3. Genotype polymorphism frequencies

3.3.1. Polymorphism of codon F31I. Table 1 shows the frequencies for heterozygote phenylalanine/isoleucine (Phe/Ile) and homozygote isoleucine/isoleucine (Ile/Ile). The

frequency of Phe/Ile was 70 (70%) and 82 (82%) in patients and healthy controls, respectively, whereas (Ile/Ile) was 30 (30%) in patients and 18 (18%) in healthy controls. This indicates an association between cancer risk and high Ile/Ile/low Phe/Ile frequencies compared with control ($P=.047$). There was no phenylalanine/phenylalanine (Phe/Phe) genotype. Figure 2 shows examples of ethidium bromide-stained gels illustrating PCR-RFLP assessment with restriction enzyme *ApoI* of the F31I codon with examples of heterozygote Phe/Ile and homozygote Ile/Ile.

3.3.2. Polymorphism of V57I. There was a higher homozygote valine/valine (Val/Val) in patients compared with controls (76% vs 68%), whereas the frequency of heterozygous Val/Ile genotype was lower in patients (17%) than controls (30%), yielding a marginal association between breast cancer and high Val/Val and low Val/Ile genotype, compared to controls ($P=.048$). Higher cancer risk in terms of OR (95% CI) was 1.9723

Table 1

The frequency of genotype polymorphism of codons F31I and V57I of *AURKA* gene in case and control samples.

Polymorphism	Cancer n, %	Control n, %	Total
Codon F31I genotype			
Phe/Ile (phenylalanine/isoleucine)	70 (70%)	82 (82%)	152
Ile/Ile (isoleucine/isoleucine)	30 (30%)	18 (18%)	48
Phe/Phe (phenylalanine/phenylalanine)	0	0	0
Codon V57I genotype			
Val/Val (valine/valine)	76 (76%)	68 (68%)	144
Val/Ile (valine/isoleucine)	17 (17%)	30 (30%)	47
Ile/Ile (isoleucine/isoleucine)	7 (7%)	2 (2%)	9

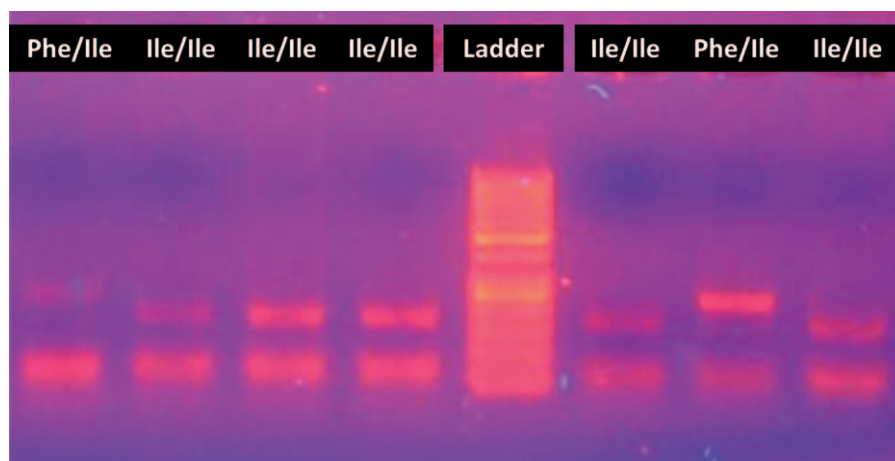


Figure 2. PCR-RFLP products lines for F31I codon after adding ApeI enzyme. The PCR product total length was 230 bp total length. The length of the cut sections were 75 and 155 bp. Ladder was 50 bp for PCR-RFLP. PCR = polymerase chain reaction, PCR-RFLP = polymerase chain reaction restriction fragment length polymorphism analysis.

(1.0002–3.8893) for high Val/Val and low Val/Ile in cancer group compared with controls.

The homozygous Ile/Ile genotype was found in 7 (7%) and 2 (2%) of patients and healthy controls, respectively (Table 1). Association of this genotype with cancer could not be tested because of small numbers.

Figure 3 shows BstUI digestion products for the V57I codon. Restriction fragments for heterozygote Val/Ile and homozygote Val/Val are shown. Figure 4 demonstrates BstUI restriction fragments of the PCR products for V57I codon showing heterozygote Val/Ile and noncut homozygote Ile/Ile genotypes.

3.4. Association of tumor grade and stage with polymorphisms of F31I and V57I

No significant associations existed between the F31I or V57I genotypes and carcinoma grade (Table 2). There was however a statistically significant association between F31I polymorphism and stage of cancer, indicating lower frequency of Phe/Ile genotype and higher frequency of Ile/Ile at the more advanced

tumor stage ($P=.019$, P for trend=.003). No significant association between V57I genotype and stage was observed.

3.5. Follow up and surviving rate

All cases with invasive ductal carcinoma were followed up for a minimum of 30 months (Fig. 5). There was no significant association between survival and any specific genotype in codon V57I. However, mean survival was worse for patients who were homozygote for Ile/Ile in codon F31I compared with other genotypes [20.9 (95% CI: 14.1–27.7)].

4. Discussion

Genetic and epigenetic factors influencing breast cancer risk include polymorphisms involving genes, including *AURKA*. Allele frequencies vary in different human populations. Despite wide investigation, the contribution of *AURKA* V57I and F31I polymorphisms to breast cancer risk is still controversial:

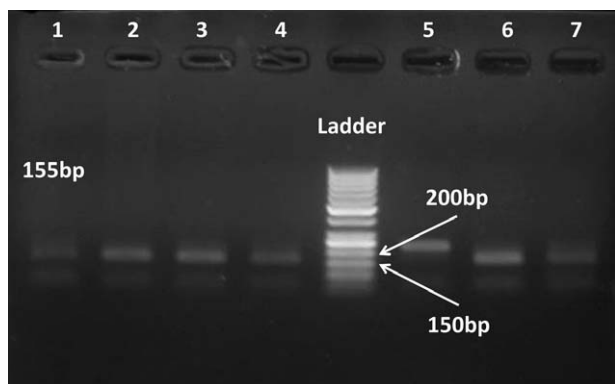


Figure 3. PCR-RFLP products lines for V57I codon after adding BstUI enzyme. Note the restriction fragments for heterozygote Val/Ile and homozygote Val/Val. Bands 1 to 7 are PCR products of cancer specimens. PCR = polymerase chain reaction, PCR-RFLP = polymerase chain reaction restriction fragment length polymorphism analysis.

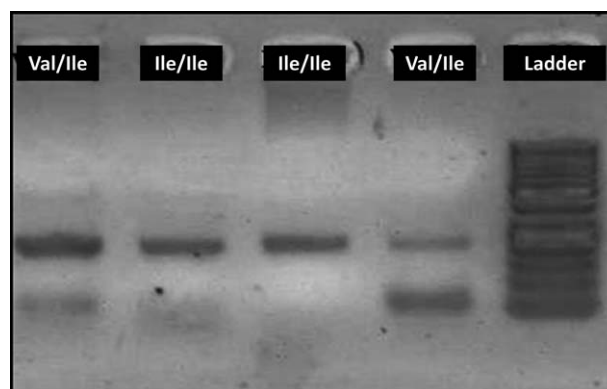


Figure 4. PCR-RFLP products lines for V57I codon after adding BstUI enzyme. Note the length of cuts after digestion for heterozygote Val/Ile, and noncut homozygote Ile/Ile. The PCR product total length was 230 bp. The length of the cut sections were 65 and 165 bp. PCR = polymerase chain reaction, PCR-RFLP = polymerase chain reaction restriction fragment length polymorphism analysis.

Table 2**Histological characteristics of breast cancer associated with polymorphisms of F31I and V57I in *AURKA* gene.**

Characteristics	F31I		V57I		
	Phe/Ile n, %	Ile/Ile n, %	Val/Val n, %	Val/Ile n, %	Ile/Ile n, %
Stage of cancer					
0/I	30 (43%)	7 (23%)	29 (38%)	6 (35%)	2 (29%)
II	28 (40%)	11 (37%)	30 (39%)	7 (41%)	2 (29%)
III	9 (13%)	4 (13%)	10 (13%)	2 (12%)	1 (14%)
IV	3 (4%)	8 (27%)	7 (9%)	2 (12%)	2 (29%)
Statistical significance	$\chi^2 P$ value = .019; P for trend = .003			NS	
Grade of tumor					
1	12 (17%)	7 (23%)	16 (21%)	3 (18%)	0 (0%)
2	40 (57%)	11 (37%)	42 (55%)	7 (41%)	2 (29%)
3	18 (26%)	12 (40%)	18 (24%)	7 (41%)	5 (71%)
Statistical significance	NS			NS	

conflicting results mean any definite association between either *AURKA* V57I or F31I and breast cancer remains elusive.

AURKA helps to maintain chromosome integrity after DNA damage.^[20] A role for nonsynonymous *AURKA* polymorphisms in carcinogenesis is at least mechanistically plausible.^[21,22] Nikonova et al showed association of overexpression of *AURKA* with defective mitotic spindles, supernumerary centrosomes, chromosomal instability, aneuploidy, and apoptosis resistance.^[5]

In Finland, Staff et al reported *AURKA* overexpression in 21% of 126 patients with breast cancer.^[15] Overexpression of *AURKA* is associated with autophagy inhibition^[23] and Taxol resistance in breast cancer.^[24] Studies in Chinese Han population showed associations between *AURKA* polymorphisms and breast cancer risk; the association was stronger when another polymorphism in *BRCA1* was present.^[22]

A meta-analysis of 14 case-control studies of cancer susceptibility comprising 11,245 cases, and 16,024 controls suggested a protective effect of *AURKA* V57I polymorphism, especially in Caucasians, rather than Asians; analysis by ethnicity indicated a decreased risk of breast cancer in Caucasians specifically. However, even the large sample size did not provide enough statistical power for definitive conclusions.^[25]

King et al claimed a role in mammary carcinogenesis for the F31I polymorphism, but not for V57I.^[26] Qin et al showed that the F31I Ile/Ile allele predisposes Asians and Caucasians women to breast cancer, but found no significant association between the V57I polymorphism and breast cancer risk.^[27] In contrast, Fletcher et al found no consistent association between breast cancer risk and the F31I polymorphism in white women of British descent. However, their results may reflect the potential geographic-dependent genetics risk factors in the UK. Additionally, statistically significant heterogeneity in odds ratio estimates may reflect population-specific linkage disequilibrium with a functional variant or artifacts, including population stratification or publication bias.^[28]

These conflicting findings suggest that other factors may modify associations between F31I and V57I *AURKA* polymorphisms and breast cancer, which could be regional dependent. In interpretation of results, we should acknowledge that these studies in different regions had different sample size and method of analysis, and did not include all life-style and environmental factors, including diet, physical activities, and various exposure to hormone replacement therapy. If there is any consensus, it is that the F31I polymorphism does modify breast cancer risk. Tang

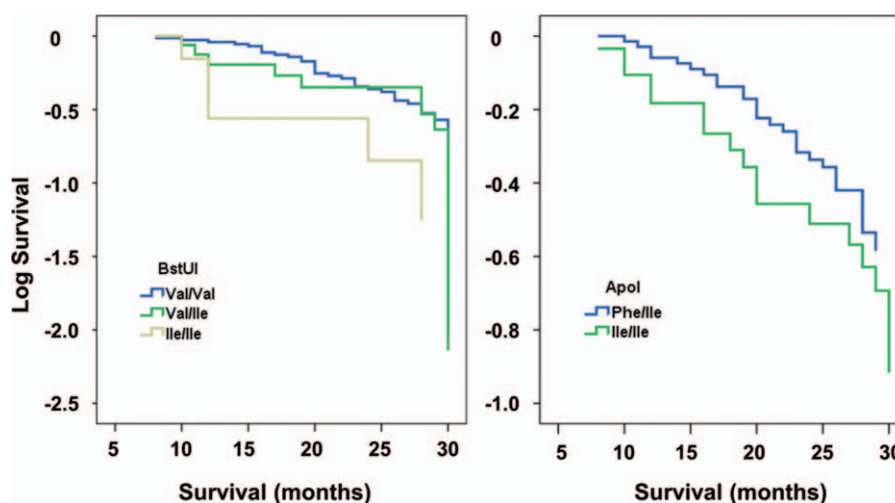


Figure 5. Association between patients' survival and single nucleotide in codon V57I (left) or codon F31I (right). Note only patients with Ile/Ile genotype in codon V57I had significantly worst survival rate.

et al in their meta-analysis study of 19,267 cancer cases and 24,359 controls supported this conclusion concerning the F31I polymorphism and breast cancer.^[29]

The main goal of our study was to examine association (if any) between the cancer risk and polymorphisms of AURKA F31I and V57I codons in the North-East Iran. Our results were in agreement with most of aforementioned studies and showed a higher frequency for homozygous Ile/Ile genotypes at the F31I locus in patients with breast cancer compared to healthy controls in North-East Iran. To the best of our knowledge, it is the first report to find an association between F31I Ile/Ile homozygosity and breast cancer in the Middle East. It is possible that the higher incidence of invasive ductal carcinoma in this area could be linked to a higher frequency of the Ile coding allele at F31I genotype. We also observed a significant association between the Ile/Ile F31I genotype and higher stage of breast carcinoma in our patients. Ruan et al reported an association between homozygote (Ile/Ile) genotype of F31I codon (rs2273535) and significant increased risk of breast cancer among the Chinese Han population.^[22] Dai et al showed elevated risk of breast cancer in association with Phe/Ile and Ile/Ile genotypes at codon 31 of the AURKA gene.^[30] They also found an association between breast cancer risk, obesity, and Ile/Ile homozygosity. In another study in which Caucasians were recruited Dai and colleagues reported the same link between F31I polymorphism and risk of breast cancer, but not for V57I.^[19]

To explore the mechanism of the AURKA gene mutations in the development and progression of the breast cancer, a new study suggested that AURKA protein kinase is involved in vasculogenic mimicry of cancer stem cells and may become a new treatment target in suppressing vasculogenic mimicry and metastasis of breast cancer.^[31]

Our study also showed that patients with the shortest survival had more homozygote Ile/Ile in codon F31I and had higher tumor stages compared with other cases, supporting an association between breast cancer and homozygote Ile/Ile genotypes at AURKA codon 31.^[21] Of course, many other factors influence breast carcinogenesis, including hormone receptors and TP53 with its important role in apoptosis.

Further studies with larger sample size and longer follow-up can be justified to let us address outstanding controversies in this area. Breast cancer risk stratification is important for earlier detection and more effective treatment. Economic and cultural obstacles to effective breast cancer management also need to be addressed.

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